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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,828	LI ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (see 2/8/07 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/18/07 has been entered. Claims 1-22 were pending. Applicants amended claim 1. No claims were added or canceled. Therefore, claims 1-22 are pending and examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

3. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. (WO 00/04196) (Date of Patent is **January 27, 2000**) (see 3/11/04 IDS) and Morris et al. (US Patent No. 6,458,530)(Filing Date is **April 4, 1996**) (of record).

For ***claim 1***, Kauffman et al. (see entire document) disclose "cis acting nucleic acid elements and methods of use" (e.g., see Kauffman et al., title and abstract), which

reads on the claimed invention. For example, Kauffman et al. disclose a library of nucleic acid constructs, each construct comprising a cis element sequence comprising one or more copies of a cis element to which a transcription factor is known to bind (e.g., see claim 38, A plurality of isolated nucleic acid molecule [i.e., a library], each isolated nucleic acid molecule comprising one or more cis acting nucleic acid elements"; see also page 1, lines 29-30, "As an example, regulatory proteins called 'transcription factors' bind to cis acting nucleic acid elements"; see also page 2, line 5; see also page 14, last paragraph; see also page 9, paragraph 2; see also pages 5-6). Kauffman et al. also disclose variation within the cis element sequence (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all [i.e., known and unknown] possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page 50, first full paragraph; see also page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known."). Kauffman et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see page 9, last paragraph, "A cis acting nucleic acid element can be localized within the nucleic acid sequence it regulates, or upstream or downstream thereof"; see also page 3, paragraph 1). Kauffman et al. also disclose a reporter sequence that is 3' relative to the promoter sequence (e.g., page 14, first full paragraph, "If desired,

some or all of the isolated nucleic acid molecules can ... be flanked at one or both ends [i.e., both 3' and 5'] by ... detectable sequences [i.e., reporter molecules]"; see also paragraph bridging pages 50-51, "... a plurality of isolated nucleic acid molecules containing cis acting nucleic acid elements can be ... enhancers and promoters ... or any other set of nucleic acid cis acting elements"). Finally, Kauffman et al. also disclose cis element sequences that "correspond" to a given reporter sequence within the library of nucleic acid constructs (e.g., see page 14, first full paragraph; see also paragraph 19, lines 13-14; see also page 34, middle paragraph; see also page 35, paragraphs 1-3; see also page 60 paragraph 1 which disclose numerous methods of detection using reporter sequences that "correspond" to the cis element i.e., allow identification of the cis element).

For ***claim 2-3***, Kauffman et al. disclose the use of conserved priming sequences (e.g., see page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can include, or be flanked at one or both ends by, known sequences, such as sequences homologous to oligonucleotide primers for the polymerase chain reaction (PCR); see also page 25, last paragraph; see also page 33, first paragraph").

For ***claims 4-7***, Kauffman et al. disclose 10^{13} different cis elements (e.g., see page 13, line 25).

For ***claims 8-10***, Kauffman et al. disclose at least two copies of the cis element (e.g., see claim 38, "A plurality of isolated nucleic acid molecules, each isolated nucleic acid molecule comprising one or more [i.e., two, three, four, etc.] cis acting nucleic acid elements"; see also page 57, lines 24-25).

For ***claims 11-13***, Kauffman et al. disclose cis elements with a length between 5 and 50 base pairs (e.g., see page 10, first full paragraph, "A cis acting nucleic acid element is generally from about 4 to about 100 nucleotides in length, and is more typically from about 6 to about 25 nucleotides in length").

For ***claim 20***, Kauffman et al. disclose different reporter sequences that encode different reporter proteins (e.g., see page 3, paragraph 1; see also page 47, paragraph 1; see also column 6, paragraph 3, "see column 3, lines 46-53, "The methods are advantageous in providing a means for simultaneously identifying nucleic acid binding factors that modulate a genetic activity of a plurality of nucleic acids").

The prior art teaching of Kauffman et al. differs from the claimed invention as follows:

For ***claim 1***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the use of a variable region within the reporter sequence nor does Kauffman et al. teach that each cis element sequence must correspond to a different reporter sequence within the library of nucleic acid constructs. Kauffman et al. only teach the use of the same reporter sequence.

For ***claims 14-19***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the size of the variable sequence in the reporter e.g., at least 14 bases in length (see claim 14).

For ***claims 21-22***, the prior art teachings of Kauffman et al. do not explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see column 23,

line 48).

However, Morris et al. teach the following limitations that are deficient in Kauffman et al.:

For ***claims 1 and 14-19***, Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, both Morris et al. and Kauffman et al. do not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et

al. with the cis acting nucleic acid library as taught by Kauffman et al. because Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. i.e., the references represent analogous art (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Kauffman. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Kauffman et al. teach the use of "cloning" techniques to produce the nucleic acid libraries (e.g., compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical

synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Furthermore, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip).

Alternatively, the Examiner contends that the mere substitution one reporter for another, which are both known in the art for labeling nucleic acids, would lead to the same predictable result in this case, namely, identification of the cis-elements. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see above) such a substitution would still be obvious in light of the Supreme Court *KSR* decision. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims

and/or arguments.

[1] Applicants argue, "The references do not teach every element of the claims ... the references, alone or in combination, provide no information at all regarding any specific transcription factors or the particular cis acting sequences to which they bind, it is quite apparaten that the combination of references is completely insufficient to provide the elements of the claimed invention. Although Kauffman discusses cis elements and transcription factors, it gives no indication regarding how to identify and select a group of cis elements" (e.g., see 5/18/07 Response, pages 5 and 6, especially page 6, first full paragraph).

[1] The Examiner respectfully disagrees. As noted in the last office action, Kauffman et al. "inherently" disclose all [i.e., both known and unknown] possible cis acting nucleic acid elements up to about 20 nucleotides in length [i.e., that are different]" (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page 50, first full paragraph). In addition, Kauffman et al. also disclose the use of "known" biased libraries (e.g., see Kauffmann et al., page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known."). Furthermore, the Examiner notes that whether Kauffman discloses a method regarding "how to identify and select a group of cis elements" is

irrelevant. Applicants are claiming a product, not a method.

[2] Applicants argue, "the reference does not teach cis element sequences that bind to specified transcription factors" (e.g., see 5/18/07 Response, page 6, last paragraph).

[2] First, the Examiner notes that the "specified" transcription factors have not been specified (at least with regard to their identity) and, as a result, Applicants' arguments are moot. Furthermore, as stated above, the disclosure by Kaufman inherently discloses ALL possible cis acting elements, which would encompass ALL known "specified" sequences. Furthermore, the biased libraries necessarily include sequences that bind to "specified" transcription factors.

[3] Applicants argue, "the reference does not provide a library of nucleic acid constructs in which each of the constructs binds to a transcription factor ... Because the cis acting sequences of Kauffman include sequences that bind to things other than transcription factors and the claimed invention comprises a library of constructs wherein every construct binds to a transcription factor, Kauffman does not teach every element of the claimed invention" (e.g., see 5/18/07 Response, paragraph bridging pages 6 and 7).

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "each of the constructs bind to specified transcription factors") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants' use of open-ended "comprising" terminology would not preclude the

addition of member that do not bind to specified transcription factors. In addition, the "biased" libraries noted above fulfill this requirement.

[4] Applicants argue, "A teaching that a nucleic acid between 5 and 20 nucleotides in length of any combination of naturally occurring nucleotides, while technically including every possible nucleic acid of that length, is not sufficient to teach a particular subset of nucleic acids" (e.g., see 5/18/07 Response, page 7, last paragraph).

[4] See Response [3] above.

[5] Applicants argue, "This detectable element [disclosed in Kauffman] is not a corresponding reporter in the sense of the claimed invention; it does not correspond to a particular cis-element ... all the detectable tags in Kauffman are identical to each other and can merely detect the presence of a cis acting element, not a particular cis element" (e.g., see 5/18/07 Response, page 8, middle paragraph).

[5] In response to applicant's arguments against the Kauffman et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach the use of detectable elements that correspond to a particular cis element. For example, Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic

acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7), which when combined with the teachings of Kauffman et al. would provide "different" sequences that "correspond" to "each" cis-element containing library member.

[6] Applicants argue, "The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which are used in different ways cannot be combined to produce one nucleic acid with two variable regions that vary dependently or correspond to each other as claimed ... Neither reference teaches the addition of a variable reporter to a nucleic acid that already has a variable cis element region" (e.g., see 5/18/07 Response, paragraph bridging pages 8 and 9).

[6] The Examiner respectfully disagrees. Here, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would lead a person of skill in the art to the automated nucleic acid chips and associated methods [i.e., the use of variable sequence tags] as disclosed by Morris et al. because the invention of Morris et al. "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitates "massive parallel analysis" (e.g., see Morris et al., Summary of Invention). Furthermore, Applicants' implication that complications would result from the "two corresponding variable regions" is entirely unsupported (i.e., no evidence or scientific reasoning is provided) and is also inconsistent with the disclosure of Morris. For example, in order for the nucleic acid sequences

disclosed by Morris et al. to function as "tags" they must "necessarily" hybridize to their complementary sequences in the presence of a target sequence (otherwise they wouldn't function as a tag). Thus, the target sequence does not impede the hybridization as purported. In addition, there is no evidence to suggest that the "cis element target sequence" disclosed by Kauffman et al. would act any differently than the target sequences mentioned above. To the contrary, less complications would be produced because the uniform hybridization techniques decrease "cross hybridization" and thus "reduce ambiguities" in high throughput screening assays (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array").

[7] Applicants argue, "When viewed as a whole ... nowhere in the prior art has such a combination been shown or suggested ... nothing in the cited references considers the concept of a single nucleic acid with these two corresponding variable regions" (e.g., see 5/18/07 Response, page 9, last two paragraphs, especially middle paragraph).

[7] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071,

5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Here, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would lead a person of skill in the art to the automated nucleic acid chips and associated methods disclosed by Morris et al. because the invention of Morris et al. "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitates "massive parallel analysis" (e.g., see Morris et al., Summary of Invention). Thus, the purpose of finding new cis elements and/or cis element binding factors/inhibitors/drugs has not been "defeated" as purported by Applicants, but "augmented" as set forth above. In addition, the Examiner notes that the Kauffmann et al. reference is not limited to a method for identifying "new" cis elements as purported by Applicants (e.g., see page 42, last paragraph, "The isolated nucleic acid molecules ... in the exemplary methods of identifying therapeutic compounds ... can be biased populations that include cis acting nucleic acid elements ... that are known"; see also Detailed Description of Invention wherein many embodiments are disclosed).

With regard to Applicants' "reference as a whole" argument the Examiner notes that Applicants' position is not entirely clear. For example, Applicants have not alleged that the Examiner has impermissibly boiled the claimed invention down to a "gist" or a "thrust" of the invention as was shown to be improper in cases like Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447-49, 230 USPQ 416, 419-20 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987); Jones v. Hardy, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984); and Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.),

cert. denied, 481 U.S. 1052 (1987). See, for example, MPEP § 2141.02, section II. To the contrary, all claimed limitations have been addressed in great detail as set forth in the rejection above. In addition, Applicants have not alleged or provided any evidence showing a failure to discover a source/cause problem, nor have they suggested that the Examiner has failed to appreciate certain "inherent" features. See, for example, MPEP § 2141.02, sections III-V. Finally, the Examiner notes that have failed to set forth any "teaching away" argument. See MPEP § 2141.02, section VI. Therefore, Applicants' arguments amount to an unsubstantiated assertion that has not been adequately explained.

[8] Applicants argue, "There is nothing in Kauffman or Morris to suggest or motivate the combination of references at issue ... The Examiner relies on a quote in Kauffman stating that, 'nucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis—acting nucleic acid element' .... The claimed invention is not about 'identifying cis acting nucleic acid elements.' Therefore, the quote cannot provide a motivation to produce the claimed invention" (e.g., see 5/18/07 Response, page 10).

[8] With regard to Applicants' "no motivation" argument, see section [7] above. In addition, the Examiner notes, "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention" (see MPEP § 2144). Thus, it does not matter whether Applicants' were not motivated to identify cis acting nucleic elements. Furthermore, the Supreme Court recently noted that the mere substitution of one element for another to yield predictable results would likely be held to obvious whether an explicit motivation was provided

or not. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007). Here, the mere substitution of variable tags disclosed by Morris et al. for the reporters disclosed by Kauffman et al. would lead to the same predictable result, namely, identification of the cis-element. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see above e.g., enables massive, cost-effective parallel screening), such a substitution would still be obvious in light of the *KSR* decision.

[9] Applicants argue, "Another motivation alleged for combining Morris and Kauffman is to make a more efficien process ... [to] recud[e] unwanted hybridization between probes. Applicants questions whether the more efficient process motivated by this statement is a process as described in Kauffman or a process as described in Morris. The suggestion must come from the references (or at least the prior art) and not simply from the present application ... The claims are not drawn to a process, so again Applicants question whether the motivation put forth in the rejection regarding a more efficient process is even relevant to the claimed invention, especially given that the claimed nucleic acid libraries would have no use in either of the process described in the two references" (e.g., see 5/18/07 Response, page 11, paragraphs 1 and 2).

[9] To the extent that this Argument is understood, the Examiner notes that Applicants have already acknowledged that the alleged motivation comes from the prior art (i.e., Morris reference) and the Examiner has provided the specific page and line number for this citation. Thus, it is unclear how Applicants can argue that the motivation comes from their specification when they have already admitted that it does not. In addition, whether Applicants claimed invention could be bodily incorporated into one of the references (i.e., Morris or Kauffman) is

irrelevant. As noted above, "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention" (see MPEP § 2144). See also *KSR* discussion above.

[10] Applicants argue, "The last allegation regarding motivation to combine is that the two references are both drawn to 'expression' methods for use in the creation of nucleic acid libraries. This does not provide a sufficient or particular motivation to combine these two specific references. For example, what specific motivation would lead someone to select these two references from the 34,272 patentes that turn up in a US patent search for the terms 'expression' and 'library.'

[10] The Examiner respectfully contends that Applicants' have misinterpreted this portion of the rejection. The Examiner never alleged that the mere fact that both references are drawn to "expression" methods provides motivation to combine. To the contrary these statements were placed in the "reasonable expectation of success" section. Thus, Applicants' arguments are moot. To prevent further confusion, the Examiner has amended this portion of the rejection to further clarify the position.

[11] Applicants argue, "the Examiner has not stated how the combination of references is even to be achieved ... It is completely unclear even how the various protocols of Morris are to provide a nucleic acid construct that correlates a particular transcription factor with a particular reporter" (e.g., see 5/18/07 Response, page 12, firs full paragraph).

[11] It is respectfully submitted that the prior art references provide adequate guidance in

this respect. For example, Morris et al. expressly disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries, which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7; see also column 4, lines 29-43, "In one class of embodiments, the invention provides a method of labeling a composition, comprising associating tag nucleic acid with the composition ... As described herein, preferred compositions include constituents of cellular, viral or molecular libraries [i.e., the libraries disclosed by Kauffman]"). Thus, a person of ordinary skill in the art could easily label the cis-acting molecular library disclosed by Kauffman using the techniques disclose by Morris.

[12] Applicants argue, "No expectation of success exists ... The combination of references does not even remotely provide the limitations of the claims; there is no specific motivation to make the combination of references ... Applicants ask a simple question; which of the 10^{13} sequences of Kauffman are to be used with the reporters of Morris to provide a library specific to transcription factors as claimed? A library comprises of the 10^{13} sequences of Kauffman would not be a very efficient library for the identification of transcription factors and not teaching or suggestion is provided for how to select those members of the groups that would make a successful library for such a use. Therefore, no expectation of success is provided in the references" (e.g., see 5/18/07 Response, page 12, last paragraph).

[12] First, the Examiner notes that Applicants have confused and/or mismatched arguments. The above excerpt tries to combine all of Applicants' previous arguments with

respect to motivation, claim limitations, etc. under the new "reasonable expectation of success" argument without providing any further why a person of ordinary skill in the art would not reasonably expect to be successful. To the extent that Applicants' argument on this latter point can be gleaned from this compilation of unrelated statements the Examiner notes as in the rejection above, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Kauffman et al. teach the use of "cloning" techniques to produce the nucleic acid libraries (e.g., compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Furthermore, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip). In addition, the Examiner notes that none of the statements mentioned in this passage refute these assertions. With regard to Applicants' other arguments, the Examiner contends that the motivation, claim limitations etc. were adequately addressed the above section.

Accordingly, the above 35 U.S.C. § 103(a) rejection is hereby maintained.

5. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (WO

00/34435) (Date of Patent is **June 15, 2000**) and Morris et al. (US Patent No. 6,458,530) (Filing Date is **April 4, 1996**) (of record).

For ***claims 1, 4, 5, 8-10, 11-13, and 20***, Li et al. teach all the limitations stated in the 35 U.S.C. 102(b)/103(a) rejection below (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 1, 4, 5, 8-10, 11-13 and 20. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

The prior art teachings of Li et al. differ from the claimed invention as follows:

For ***claims 2-3***, Li et al. fail to disclose "priming sequences" 5' and 3' to the variable sequences.

For ***claims 6-7***, Li et al. fail to disclose a library with at least 50 cis elements. Li et al. only disclose a library of 33 cis elements.

For ***claims 14-19***, Li et al. fail to disclose the size of the variable sequence in the reporter.

For ***claims 21-22***, Li et al. fail to explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see figures and Examples).

However, Morris et al. teach the following limitations that are deficient in Li et al.:

For ***claim 1***, Morris et al. (see entire document) additional disclose specially

selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7). Thus, even if Li et al. did not anticipate the claimed invention as set forth in the 35 U.S.C. §§ 102/103(a) rejection below (which is not the case), the claimed invention would still be obvious in vie of Morris et al. for the reasons stated herein.

For ***claims 2-3***, Morris et al. disclose priming sites 5' and 3' to the reporter sequences (e.g., see figure 5 caption, "Tags were amplified using a single pair of primers that are homologous to the common priming sites which flank each tag [i.e., 5' and 3']").

For ***claims 6-7***, Morris et al. disclose "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would render obvious larger numbers of constructs in order to "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate"; see also column 4, first full paragraph, "In preferred embodiments, the set of tag nucleic acids comprises from 100-100,000 tags. Typically, a tag set will include between about 500 and 15,000 tags. Usually, the number of tags in a tag set is between about 5,000 and about 14,000 tags")

For ***claims 14-19***, Morris et al. disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries that would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, Morris et al. does not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid libraries as taught by Li et al. because Morris et al. explicitly state that their sequences can be used to track, for example, recombinant cells in high throughput screening assays (e.g., see Morris et al., "This invention provides sets

of nucleic acid tags, arrays of oligonucleotide probes, nucleic acid-tagged sets of recombinant cells ..."), which would encompass the recombinant cells disclosed by Li et al. (e.g., see Li et al., Example 4, "A set of d2EGFP reporters with different cis-elements were generated, which are used for monitoring different transcription factors. Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening"; see also Example 5, "cell clones can be used in cell based high-throughput screening in search of factors involved in cAMP signal transduction pathway"). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a

VLSIPS™ array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods that can used to create the libraries (e.g., see Morris et al., column 20, last paragraph, "Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also Li et al., Summary of Invention, "In yet another embodiment of the present invention, there is provided a method of monitoring activation of a transcription factor, comprising the steps of ... transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor").

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The references do not teach every element of the claims ... there is

no library of constructs in Lid wherein each nucleic acid comprises two variable sequences that vary dependently with each other. Although different reporters exist and different cis-elements exist, there is no teaching or suggestion regarding a combination of these constructs as presently claimed, wherein each cis-element sequence has a different reporter that corresponds to a particular cis element/transcription factor pair" (e.g., see 5/18/07 response, page 13, especially last full paragraph).

[1] In response to applicant's arguments against the Li et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach the all of the claimed limitations as set forth in the rejection above. Substituting the random tags as disclosed by Morris et al. for the reporters as disclosed by Li et al. would clearly provide different reporters for each of the cis element/transcription factor pairs. Thus, one reporter would "correspond" to one cis element by its covalent attachment to that element.

Furthermore, the Examiner notes that Li et al. anticipates the claimed invention with respect to claims 1, 4, 5, 8-10, 11-13 and 20 rendering all of Applicants' 35 U.S.C. § 103(a) arguments moot with respect to these claims.

[2] Applicants argue, "The combined references do not teach every element of the claimed invention because neither reference teaches a single nucleic acid construct with two variable elements that correspond to each other – a cis element and a reporter" (e.g., see 5/18/07 Response, paragraph bridging pages 13 and 14).

[2] The Examiner respectfully disagrees. Li et al. teach both elements by itself as set forth in the 35 U.S.C. § 102 rejection below. Furthermore even if, *assuming arguendo*, Li failed to teach this element (which is not the case, see 35 U.S.C. § 102/103 rejection below), Morris et al. would still provide the alleged missing element. Specifically, Morris et al. disclose selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Li et al. That is, Li et al. disclose a library of nucleic acid constructs wherein each construct comprises a cis-element that varies within the library (e.g., see Li et al., pages 9 and 10, Example 1; se also figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc) and when combined with the teachings of Morris et al. also "variable sequence" reporters (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

In addition, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a single nucleic acid construct with two variable elements") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The only claimed element with a "variable" region is the reporter.

[3] Applicants argue, "The reporter activity in Lid corresponds to the presence or absence of a cis element; it gives no information regarding the type of cis element present because no correspondence or association exists between a particular cis element and a reporter" (e.g., see 5/18/07 Response, page 14, paragraph 1).

[3] The Examiner respectfully disagrees. The reporter corresponds to the cis-element that is covalently attached to. Therefore, it will necessarily provide information about the cis-element that it is covalently attached to. Applicants' claimed scope requires nothing more. See 35 U.S.C. §§ 102/103 rejection below.

[4] Applicants argue, "there are multiple possible definitions for the term 'library,' they all allude to some type of collection ... the alleged library of Li merely comprises multiple individual nucleic acids constructs ... The individual constructs do not form a collection ... Therefore, the cited references do not teach every element of the claimed invention" (e.g., see 5/18/07 Response, page 14, first full paragraph).

[4] The Examiner respectfully disagrees. For example, Li et al. disclose a collection of constructs (i.e., a library) on 12 or 24 well plates as set forth in Example 8. See also figure 4.

[5] Applicants argue, "The motivation to combined the references is lacking in this rejection ... Part of the inventive concept presently claimed is putting two variable sequences (a cis element and a reporter) on the same nucleic acid construct and having them correspond to each other ... Only a hindsight argument using the present claim as a blueprint can take a variable sequence in one application and combine it with an unrelated individual construct in a totally different application" (e.g., see 5/18/07 Response, paragraph bridging pages 14 and 15).

[5] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so

long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the

invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS™ array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array").

Finally, with respect to claims 1, 4, 5, 8-10, 11-13 and 20 Applicants' arguments are moot because Li et al. anticipates the claimed invention (e.g., see 35 U.S.C. §§ 102/103 below).

[6] Applicants argue, "The particular motivation espoused by the rejection is that both references involve expression and cloning ... ." (e.g., see 5/18/07 Response, page 15, paragraph 2).

[6] The Examiner respectfully submits that Applicants have misinterpreted this aspect of the rejection. The "expression and cloning" recitation falls under the "reasonable expectation of success" portion of the rejection, not the "motivation" section as erroneously purported. Therefore, Applicants' arguments are moot.

[7] Applicants argue that there is no expectation of success stating, "The rejection has not stated how the two unrelated variable sequences would be combined to form a library of nucleic acid transcription factor probes" (e.g., 5/18/07 Response, page 15, last paragraph).

[7] One of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods that can used to create the libraries (e.g., see Morris et al., column 20, last paragraph, "Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids

are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also Li et al., Summary of Invention, "In yet another embodiment of the present invention, there is provided a method of monitoring activation of a transcription factor, comprising the steps of ... transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor").

Furthermore, Morris et al. expressly disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries, which would encompass the nucleic acid constructs of Lid et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7; see also column 4, lines 29-43, "In one class of embodiments, the invention provides a method of labeling a composition, comprising associating tag nucleic acid with the composition ... As described herein, preferred compositions include constituents of cellular, viral or molecular libraries [i.e., the libraries disclosed by Kauffman]"). Thus, a person of ordinary skill in the art could easily label the cis-acting molecular library disclosed by Li using the techniques disclose by Morris.

Accordingly the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections – 35 U.S.C. 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 4-5, 8-10, 11-13 and 20 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Li et al. (WO 00/34435) (Date of Patent is **June 15, 2000**).

For ***claim 1***, Li et al. (see entire document) teach cis-element reporter constructs and uses thereof including "high throughput" screening libraries (e.g., see abstract; see also example 4), which read on the claimed invention. For example, Li et al. disclose a library of nucleic acid constructs (e.g., see figure 4A/B wherein a library of "SEAP"

constructs are disclosed including Ap1, HRE, Myc, p53, etc.). Furthermore, Li et al. disclose a cis element sequence comprising one or more copies of a cis element to which a transcription factor is known to bind (e.g., see Li et al., pages 9-10, Example 1, The following cis elements were utilized for constructing cis-acting reporters: NF-kb ... HRE ... Myc ... p53 ... [etc.]"; see also page 10, last paragraph, "In a AP1-SEAP construct, the cis element in the construct contains six copies of AP1 ... In a SRE-SEAP construct, the construct contains three copies of SRE element ... [etc.]"). Li et al. also disclose a library wherein the cis element varies within the library of nucleic acid constructs (e.g., see figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc.). Li et al. further disclose a promoter sequence 3' relative to the cis element sequence (e.g., see Summary of Invention, "In one embodiment of the present invention, there is provided a cis element-reporter construct comprising a cis element, a reporter gene and a promoter"; see also figures 1-3 showing, for example, 3' orientation of the TK promoter relative to the KB4 cis element; see also Examples). In addition, Li et al. disclose a reporter sequence that is 3' relative to the promoter sequence (e.g., see figures 1-3 showing SEAP, d2EGFP and luciferase reporters in a 3' position relative to the cis element, respectively; see also Examples). Finally, Li et al. disclose a "correspondence" between each cis element sequence and a given reporter sequence within the library (e.g., see figure 4A/B, wherein the amount of SEAP activity is shown to "correspond" to the type of cis element under various conditions).

The product of Li et al. meet all of the structural limitations of the claimed product (see above) except for the product-by-process limitations (i.e., the

"randomization" process used to make the variable reporter sequence) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a library of sequences (i.e., a product), but are defined (implicitly) by various method steps that produce said library (i.e., randomization method steps to make a variable sequence) and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was synthesized and/or prepared. That is, a "variable" reporter sequence would read on "all" reporter sequences because it would include "all" amino acid substitutions at every position. For example, the a "variable" sequence 3 amino acids long would include the sequences: AAA, GAAA, YAA, etc. leading to all possible permutations of those three amino acids. Consequently, the claimed variable sequences include the SEQP, destabilized green fluorescent protein, etc. disclosed by Lid et al. (e.g., see abstract).

For ***claim 4-5***, Li et al. disclose a library with 33 cis elements (e.g., see Example 2 and figure 4 A/B wherein 6 (AP1) + 3 (SRE) + 3 (CRE) + 3 (GRE) + 3 (HRE) + 4 (NF-

kB) + 3 (NFAT) + 6 (myc) + 2 (p53) = 33 cis elements are disclosed).

For ***claims 8-10***, Li et al. disclose a library that contains at least two copies of the cis element (e.g., see Example 2 and figure 4 A/B wherein the AP1 construct, for example, contains "six" copies).

For ***claims 11-13***, Li et al. disclose, for example, NF-kB with 40 base pairs (e.g., see Li et al., page 9, lines 6-7).

For ***claim 20***, Li et al. disclose different reporter sequences that encode different reporter proteins (e.g., see figures 1-3 disclosing SEAP, d2EGFP and luciferase, respectively).

Request for Interview

9. Applicants request for an interview is granted. Please contact the Examiner to set up a convenient time for all parties.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.

JON EPPERSON
PRIMARY EXAMINER